Vestibular Intervention Via Portable Electrical Stimulator (VIPES)

NCT04968197

August 18, 2023

IRB Minimal Risk Protocol Template

General Study Information

Principal Investigator: Gaurav N. Pradhan, PhD

Study Title: Vestibular Intervention via Portable Electrical Stimulator (VIPES)

Protocol version number and date: Version 2 and August 18th, 2023

Research Question and Aims

Hypothesis:
The efficacy of stochastic galvanic vestibular stimulation to improve balance and gait performance in individuals diagnosed with mild traumatic brain injury or experience vestibular disorders causing dizziness, impaired balance, and altered coordination.

Aims, purpose, or objectives:
To develop a wearable portable stimulator to stimulate the vestibular system and produce immediate improvements in balance, gait, and overall vestibular function for patients with balance disorders.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):
The vestibular system is an essential element of human balance, which is critical to proper stance and gait. An impaired vestibular system can cause debilitating dizziness or loss of balance leading to dangerous falls and an inability to perform normal activities of daily living. Vestibular dysfunction is both a hallmark of acute traumatic brain injury (TBI) and also a long-term problem with considerable quality of life effects for those experiencing mild TBI (mTBI). Often times, this dysfunction is due to a reduction in the signal from the vestibular system to the brain, resulting in a misrepresentation of the balance state of the individual with dysfunction. Recent and ongoing research has demonstrated that by boosting the signals produced from the vestibular system, these balance issues and the symptoms that go along with them can be alleviated.
To date, the War on Terror has claimed over 50,000 US casualties, many of which stem from an increase in wartime blast threats from improvised explosive devices (IEDs). Between 2000 and 2018, US Military personnel had experienced 383,947 cases of TBI, 315,897 of which were classified as mild TBI [1]. Nearly 30% of soldiers that are diagnosed with mild traumatic brain injury or worse experience vestibular disorders causing dizziness, impaired balance, and altered coordination that prevent their performance in reparative physical therapy, impede return to duty, and significantly reduce quality of life. Similarly, as many as 35% of civilian adults aged 40 years or older in the United States (~69 million Americans) have experienced some form of vestibular dysfunction with a further 4% (8 million) of American adults reporting a chronic problem with balance. Symptoms of chronic imbalance can have a significant impact on the ability of a disabled person to perform one or more activities of daily living (ADL), a term used for basic necessities such as bathing, dressing, or simply getting around inside the home.

Giving attention to this prevalent problem among warfighters and civilians alike, researchers have attempted to restore balance through vestibular implants, vibrotactile feedback, tongue placed biofeedback, and vibrating

insoles. Of these, the vestibular implant is the only one directly targeting the vestibular system. However, the invasive nature of such implants is unwarranted for acute symptoms and is highly risky for an older population that is more susceptible to surgical complication. The remaining approaches indirectly stimulate the central nervous system (CNS) as opposed to producing actual vestibular sensation. Further, many of the symptoms brought on by mTBI are acute in nature, where the vast majority of patients see improvement over a specific amount of time. Thus, implants, while highly beneficial for those with chronic vestibular dysfunction, simply do not fit a need for the vast majority of cases, revealing an immediate and significant need for a means to provide the same vestibular dysfunction correction as an implant via a comfortably worn, non-invasive device.

Recent work has focused on non-invasive electrical stimulation of the vestibular system, historically called galvanic vestibular stimulation (GVS), including use of electrical signals comprising filtered random noise, known as stochastic vestibular stimulation (SVS). These techniques promise a device that could address a loss of vestibular function and improve balance without the aforementioned drawbacks of other systems and the side effects of pharmacologic therapy. Complimentary, prior work performed in Aerospace Medicine and Vestibular Research Laboratory at Mayo Clinic Arizona has demonstrated several unique modes of transcutaneous GVS to: 1) induce a controlled sense of motion when none is present (**IRB#: 06-005443**), 2) provide directional vestibular cueing (**IRB#s: 09-003815, 18-005564, 19-003257**), and 3) mitigate the debilitating effects of motion sickness stemming from decoupling of the vestibular and visual cues (**IRB#s: 11-007718, 20-005763**) [2, 3]. Significant work by others has shown that introduction of stochastic vestibular stimulation creates a stochastic resonance effect, enhancing the diminished vestibular response in subjects with history of blast injury and mTBI. While SVS can help many patients with mTBI related vestibular impairment, other GVS stimulation modes may also be required depending on the location and severity of the injury and the nature of the activities being undertaken. Thus, a multi-modal vestibular stimulation approach is paramount to addressing the multi-variant problem of vestibular dysfunction and reaching the vast majority of patients that experience mTBI related symptoms. The proposed Vestibular Intervention via Portable Electrical Stimulator (VIPES) system (Figure 1) is a small, lightweight device able to deliver SVS using a comfortable electrode set on the back of the head as well as other proven modes of GVS related vestibular correction when required to mitigate motion sickness or provide auxiliary vestibular cueing.

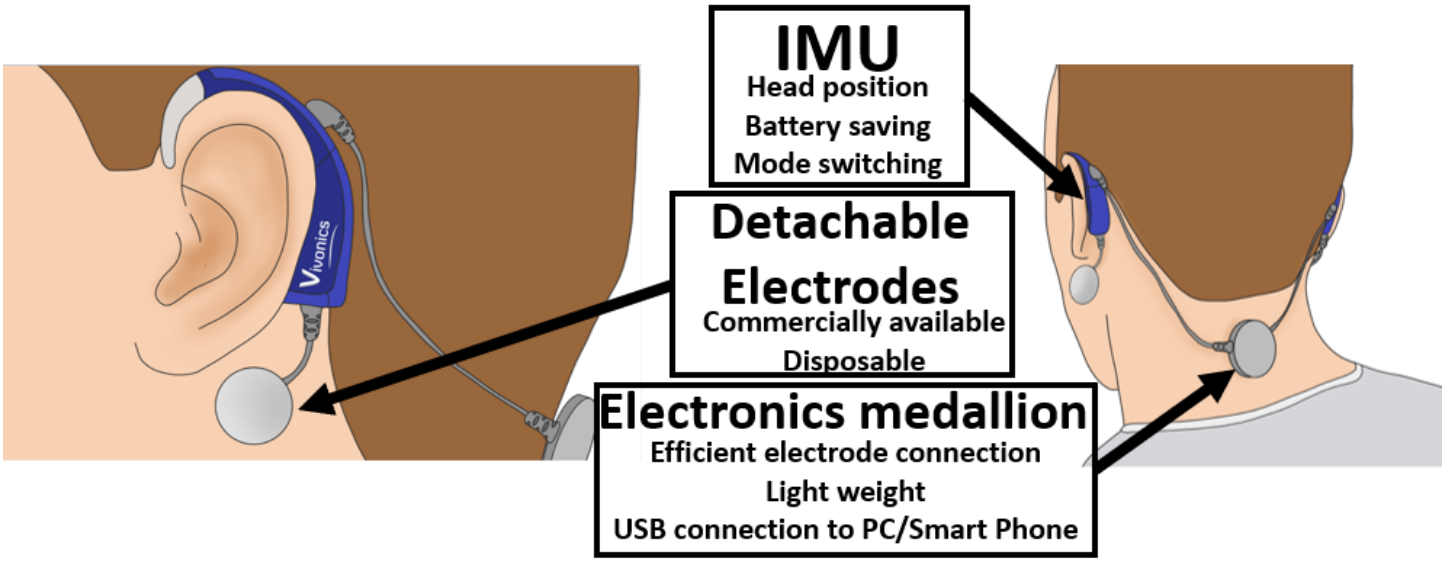

Figure 1: VIPES includes a disposable set of electrodes located behind the ears, which can be integrated into a low cost, comfortable, multi-use hearing aid style device that fits behind the ear and reports head position/motion for multi-modality control, and a small electronics / battery module that comfortably hangs down the users neck.

References:

1. DVBIC. Total (2000-2018 Q1) DoD TBI Worldwide Numbers. 2018 [cited 2019 5/29/2019]; Available from: https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi.
2. Cevette; Michael, Stepanek, Jan, Galea; Anna, Galvanic vestibular stimulation system and method of use for simulation, directional cueing, and alleviating motion-related sickness. US Patent 8,718,796.
3. Cevette, M.J., et al., Oculo-vestibular recoupling using galvanic vestibular stimulation to mitigate simulator sickness. Aviat Space Environ Med, 2012. 83(6): p. 549-55.
4. Wrisley, D.M. and S.L. Whitney, The effect of foot position on the modified clinical test of sensory interaction and balance. Archives of physical medicine and rehabilitation, 2004. 85(2): p. 335-338.
5. Massingale, S., et al., Comparison of uninjured and concussed adolescent athletes on the concussion balance Test (COBALT). Journal of neurologic physical therapy, 2018. 42(3): p. 149-154.
6. Podsiadlo, D. and S. Richardson, The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. Journal of the American geriatrics Society, 1991. 39(2): p. 142-148.

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

Consent: Consent forms include typical notifications of the sponsor and purpose of the study, identification of any risks in the minimal-risk protocol, discussion of privacy dimensions of the study and description of the amount and compensation structure schedule. We brief participants of their right to opt out of the study at any

time and for any reason. We include consent forms in the attached draft IRB that are patterned after similar forms used in other persistent sensor wear studies the Mayo team has conducted.

Compensation: Remuneration of $150 is proposed to fairly reimburse participants for the time involved.

Protocol:
In this repeated-measures design, each patient will be tested in a "*Control*", or baseline condition, and a pre-determined stimulation level of "*Stochastic Vestibular Stimulation (SVS)*" up to 1mA. In the *Control* condition: the entire testing will be conducted with the system worn but without SVS application (i.e., 0mA). The patient will be instrumented with electrodes without turning on the SVS device throughout the testing. In the SVS condition: The SVS device will be active throughout the testing at the respective current level. The test will be performed for a singular, pre-determined, GVS amplitude up to 1mA. The order of the conditions will be randomized across subjects. The details of testing (single visit) are summarized below.

Equipment:
The VIPES system that provides SVS is a small wearable device in order to improve the function of an individual's vestibular system that has been adversely affected their balance due to head injuries and mild TBI. . In particular, VIPES is designed to provide electrical stimulus comprising random noise in a low frequency band (0 to 5Hz maximum) below the level of perception by the subject. The VIPES system consists of the four electrodes (two behind each ear) similar to our commercial galvanic stimulator (Good Vibrations Engineering Ltd, King City, ON; used in the previous IRB approved projects – IRB #s: 20-005763, -19-003257, 18-005564, 14-003906, 11-007718, 09-003815). The stimulator can bidirectionally deliver the electrical stimulation and receive information about the amplitude delivered accounting for skin impedance. Bertec Portable Essential's dual-balance plate balance system *(*previously IRB approved in IRB 20-005763) used for balance testing is clinically used in Mayo Clinic Arizona.

Testing:
Following documentation of consent for study participation, participants will complete pre-testing questionnaires and medical history evaluations. Subjects will don the VIPES device and the research team will verify the system is set to 0mA and participants will then be given a direction and timeframe to walk in the Mayo Clinic space for up to 10 minutes before returning to the laboratory, as a means of establishing baseline gait, balance, stability, and pace to be measured by an incorporated accelerometer (sway score; deg/s). Once returned, participants will be allotted a 5-minute resting period prior to beginning the '*Condition*' testing. Subjects will complete a series of balance tests to establish and describe a range of balance performance. The Modified Clinical Test of Sensory Interaction and Balance (mCTSIB) [4], and COBALT Balance test [5] are measures of standing balance that increase in difficulty. These metrics will be included for the rationales noted below, but also to better describe the wide ability of balance function in individuals with balance disorder. Subjects will be randomized for balancing testing condition order and will complete the mCTSIB and COBALT with the system providing a known amount of electrical stimulus, as well as with the system providing 0mA, but will be blinded for which condition is taking place. Participants will be permitted to leave and walk normally about the premises with the VIPES system now provided the known-stimulation dose. A member of the investigational team will accompany the subjects for the duration of their walking. Subjects will return after ~30-45 mins and will be allotted an additional 5-minute resting period. Subjects will complete the mCTSIB and COBALT balance tests with the system delivering stimulation. Once completed, the VIPES system will be

removed and participants will answer the Post-Testing Questionnaires before finishing the study day and being provided remuneration. The details of testing are summarized as follows:

Visit:	Duration
Consent & Pre-Testing Questionnaire(s) • Post-concussion symptoms scale • Demographics & Medical History	10 mins
Baseline Walk • Participants will walk with the system at 0mA, as is normal, for up to 10 minutes to establish baseline gait • Subject will rest for approximately 5 minutes.	15 mins
COBALT Balance Test: *Device: Bertec Portable Essential's dual-balance plate balance system (https://www.bertec.com/bertec-balance-advantage-systems)* *Rationale:* COBALT is a balance test commonly used to evaluate individuals post-concussion. This test protocol places high demand on the visual and vestibular systems that is not provided by traditional balance tests. These higher demand conditions improve sensitivity in detecting balance dysfunction in those post-concussion. The test will be performed for a given SVS amplitude up to 1mA and 0mA, and will be randomized for each subject. Two 20-seconds trial for each of the following conditions/surfaces: On Firm Surface: • Head Shake • Visual Motion Sensitivity On Foam Surface: • Head Shake • Visual Motion Sensitivity	10 mins
Modified Clinical Test of Sensory Integration on Balance (mCTSIB): *Device: Bertec Portable Essential's dual-balance plate balance system (https://www.bertec.com/bertec-balance-advantage-systems)* *Rationale:* mCTSIB is a balance test commonly used to evaluate individuals of all ages post-concussion. This test protocol assesses how well an individual uses sensory input when one or more sensory systems are	10 mins

compromised. This protocol is commonly used to evaluate individuals post-concussion to describe static balance ability. The test will be performed for a given SVS amplitude up to 1mA and 0mA, and will be randomized for each subject. Three 10-second trials for each of the following conditions: • Standard (eyes open on firm surface) • Proprioception (eyes closed on firm surface) • Vision (eyes open on foam surface) • Vestibular (eye closed on foam surface)	
SVS Condition Walk • Participants will walk with the system at 0mA, as is normal, for up to 45 minutes to establish baseline gait • Subject will rest for approximately 5 minutes.	50 mins
Repeat mCTSIB and COBALT	20 mins
Post-testing Questionnaires: • Clinical Motion Sickness Symptom Severity • System Usability Scale (SUS) • Subjective Clinical Feedback	5 mins

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 40 participants

Subject population (adults, groups): Patients – 1) diagnosed with a balance disorder and/or having sustained a concussion and/or mild traumatic brain injury (mTBI), 2) Currently being evaluated at Mayo Clinic Arizona, 3) self-reported imbalance,

Inclusion Criteria: For our purposes, participants must be able to consent to participate themselves and be 18 to 70 years of age and must be able to attend in-person sessions at the Mayo Aerospace Medicine and Vestibular

Research Laboratory in Scottsdale, AZ. No racial/ethnic groups will be excluded, although all participants must be fluent speakers of English

Exclusion Criteria: 1) Presence of peripheral vestibulopathy (cleared by Dix-Hallpike, vHIT as part of clinical evaluation), 2) women who are pregnant, and 3), inability to complete testing (e.g., severe symptom burden, inability to stand unassisted).

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: __N/A___ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _N/A_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _N/A____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _N/A_____

Prospective collection of biological specimens other than blood: ___N/A_____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Data Analysis Plan:

We will use repeated measures ANOVA to examine changes in balance performance during balance testing by measuring sway score (i.e., sway angular velocity, deg/s) across tested levels of GVR amplitude and control condition. Sample size estimates are based on: (1) the expected variability (s2) in the response parameters, (2) the alpha (a, type I) error level, or probability of incorrectly concluding there is an effect when responses are equivalent, (3) the magnitude of the effects to be detected between the means (μ1, μ2), and (4) the certainty (statistical power, 1- b) with which the effect is to be detected. Sample sizes can be calculated based on the expected standardized differences (Δ) between conditions.

Power Statement:
Standardized mean differences of 0.08 deg/s on firm surface and 0.17 deg/s on foam surface will be considered operationally relevant effect sizes for balance performance comparison based on previous balance testing protocols using the COBALT testing [5]. Based on the equation above, we will have 80% statistical power to detect standardized mean differences (two-sided tests) of 0.08 (firm surface) and 0.17 (foam surface) with an

alpha error level of 0.05 with a sample of 22 participants. A target of at least 30 participants is requested to account for incomplete data sets.

Endpoints
Primary: Our project will deliver a vestibular interventional approach using stochastic vestibular stimulation (SVS) through a small, lightweight, and portable device housed in a body-worn torso strap that feeds into a comfortable electrode set on the back of the head (on the mastoid process) to deliver continuous and dose-specific stimulation to the vestibular system and produce immediate improvements in balance, gait, and overall vestibular function.